Case Report: A Common Presentation of a Rare Disease-Hepatosplenic T-Cell Lymphoma

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Abstract

Hepatosplenic T-cell lymphoma is a rare neoplasm characterized by systemic B-symptoms, hepatosplenomegaly, no lymphadenopathy; and lymphomatous infiltrates in the splenic red pulp, hepatic sinusoids, and bone marrow sinuses. The team presents the case of a healthy 30 year old man, active duty Marine, who presented with classic symptoms, yet obtaining a diagnosis took over three months from the onset of symptoms. This clinical entity, initially described in 1990, is elusive, with vague and misleading symptoms. Despite aggressive conventional therapy with anthracycline-based regimens and stem cell transplant, prognosis is poor and median survival is less than one year.

Introduction

Hepatosplenic γδ T-cell lymphoma (HSTCL) is a rare lymphoid neoplasm only recognized as a distinct entity in 1990[1]. This neoplasm is characterized by lymphomatous infiltration of the hepatic and splenic red pulp sinuses resulting in splenomegaly and hepatomegaly without peripheral lymphadenopathy. Since the initial classification, approximately 80 cases have been described in the literature[1, 3-14].

Case Report

History/Physical exam

A 30 year old Caucasian man who is an active duty Marine Corps officer stationed in Okinawa, Japan without significant past medical history initially presented to his local clinic with complaints of back and abdominal pain with associated intermittent fevers and diaphoresis. He was given NSAIDs and told to keep himself well hydrated. He continued to fulfill his active duty responsibilities for about two months, while his symptoms gradually worsened, with increasing abdominal and back pain, and daily fevers. At this time, he also complained of frequent loose dark stools, malaise, anorexia, and mild nausea. The abdominal pain was described as a generalized cramping without any aggravating or relieving factors and a sensation of "rock-hard abs". He was admitted to the Naval Hospital in Okinawa for massive hepatosplenomegaly and abdominal guarding.

Figure 1.— CT scan of the abdomen, demonstrating hepatomegaly and splenomegaly.

Physical examination revealed a firm abdomen with mild diffuse tenderness to palpation, liver palpable 5 cm below the costal margin, spleen palpable to the level of the umbilicus, and no peripheral lymphadenopathy. Initial laboratory evaluation revealed: white blood cell count 4.2 x 10^9/L with normal differential, normal hematocrit, platelets 98 x 10^9/L, aspartate aminotransferase (AST) 152 IU/L, alanine aminotransferase (ALT) 118 IU/L, γ-glutamyl-transpeptidase (GGT) 110 IU/L, alkaline phosphatase 182 IU/L, total bilirubin 0.9 mg/dL, INR 1.2, and lactate dehydrogenase (LDH) 3343 U/L. Given his presentation, there was concern for malignancy vs. severe infectious etiology, and the patient was air-evacuated to Tripler Army Medical Center for further evaluation.

Diagnostic evaluation

Computed tomography scan of chest, abdomen, and pelvis demonstrated (Figure 1): massive splenomegaly with a splenic index of 5400cc, (normal 460cc); hepatomegaly without intrahepatic or extrahepatic ductal dilation; inflammatory changes of the descending and

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sigmoid colon with focal areas of bowel wall thickening; and no significant lymphadenopathy. Given the colon-related findings and the patient's symptoms of loose dark stools coupled with nausea and anorexia, we pursued endoscopic evaluation to further delineate these findings/symptoms. Both esophagoduodenoscopy and colonoscopy were normal without pathologic findings. Although a malignant etiology was likely, the patient had significant travel history and thus a concurrent infectious workup was performed. At time of evaluation, he was stationed in a remote/field location on the outskirts of Okinawa, Japan. He had recently traveled to remote regions in Australia, and had previously been stationed or traveled to Korea, Kuwait, and Norwayto. Tests performed to rule out infection included: serologic test for hepatitis A, B, and C; thick and thin smears for malaria; blood, urine, and sputum cultures; monospot testing for Ebstein Barr virus (EBV); HIV; human T-cell lymphotrophic virus type I (HTLV-1), PPD testing for tuberculosis; cytomegalovirus (CMV) serologic testing; brucella, coxiella, cryptococcus, coccidioides, histoplasma, lyme disease, and typhus. . The thorough infectious evaluation only revealed IgG positivity to CMV and was otherwise negative.

During the diagnostic evaluation, he continued to suffer from daily fevers and mild abdominal discomfort, with persistent transaminitis. A bone marrow biopsy with aspiration and peripheral blood analysis was subsequently performed. The findings included: peripheral blood analysis - a mild and normochromic/normocytic anemia, with mild lymphopenia and thrombocytopenia, without circulating blasts or otherwise atypical/dysmorphic elements; bone marrow/aspirate - cellular and hematopoietically active bone marrow with megakaryocytic hyperplasia; flow cytometry - subpopulation of $CD2^+$, $CD3^+$, $CD7^+$, $CD5^-$, $CD4^-$, and $CD8^-$ lymphocytes. This subpopulation of aberrant lymphocytes was of undetermined significance. B-lymphocytes showed heterogeneous surface immunoglobulin expression. There were also viral, bacterial, fungal, and AFB cultures obtained from the bone marrow, which eventually returned negative. Chromosomal analysis demonstrated 46, XY normal male, without abnormalities.

Following the non-diagnostic bone marrow biopsy, the search for a tissue diagnosis led us to an ultrasound guided liver biopsy, and then possibly a splenectomy for symptomatic relief and diagnostic value. The liver biopsy demonstrated diffuse infiltration of an atypical lymphoid population within the hepatic sinusoids. Lymphocytes were positive for LCA (Leukocyte Common Antigen) and UCHL-1 (specific for T-cells), and negative for CD20 (B-cell receptor). These features were consistent with hepatosplenic T-cell lymphoma. Further genetic characterization was limited due to the small tissue sample obtained on initial biopsy. Subsequent evaluation and immunohistochemical staining revealed that the small subpopulation of T-cells with the aberrant phenotype ($CD4^-$, $CD5^-$, and $CD8^-$) was consistent with 10% bone marrow involvement with lymphoma. Staining showed UCHL-1 positive cells distributed intrasinusoidally throughout the marrow clot sections. Given the final diagnosis and severity of illness, the patient was transferred to a medical facility closer to his family for definitive treatment. He is undergoing a protocol at the National Institutes of Health with EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin). With chemotherapy, his spleen decreased in size and he is currently awaiting allogeneic stem cell transplant.

Table 1.— WHO/REAL Classification of Mature T-Cell and NK-Cell Neoplasms

Leukemic • T-Cell prolymphocytic leukemia • T-Cell Large Granular lymphocytic leukemia • Aggressive NK-cell leukemia • Adult T-cell leukemia/lymphoma (HTLV-1+)
Nodal/Lymphoma • Peripheral T-cell lymphoma, unspecified • Angioimmunoblastic T-cell lymphoma • Anaplastic Large-cell lymphoma (ALCL)
Extranodal/cutaneous • Indolent: Mycosis Fungoides/Sezary Syndrome Primary Cutaneous ALCL • Aggressive: Extranodal NK/T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Hepatosplenic T-cell lymphoma Subcutaneous Panniculitis-like T-cell lymphoma Blastic NK-cell lymphoma

Discussion

The clinical features described in the case report are characteristic of hepatosplenic T-cell lymphoma. This rare neoplasm only accounts for 5 percent of all peripheral T-cell lymphomas (Table1) and PTCLs are only a small portion of all non-Hodgkins lymphomas (15%)[2]. Since Farcet described this condition as a distinct entity in 1990 by, there have been approximately 80 cases reported in the literature[1, 3-14]. This uncommon lymphoma primarily affects young males with a median age of about 35 years. Patients typically present with marked splenomegaly and most often hepatomegaly, without lymphadenopathy. Most will have systemic B-symptoms including fever, night sweats, fatigue and weight loss. Predominant laboratory findings include reduced peripheral blood counts (especially thrombocytopenia), elevated LDH, and abnormal liver associated enzymes[14,15]. The diagnosis of HSTCL can be difficult, as occurred with the described patient, and can easily be missed at the outset. Reports of initial misdiagnosis include

viral hepatitis, autoimmune hepatitis, chronic myelomonocytic disorder, and idiopathic thrombocytopenic purpura, are evidence of the difficulty characterizing this uncommon disease [3-6].

The majority of cases are diagnosed at splenectomy. Less commonly, the diagnosis may occur at liver biopsy, as in our case. The typical histopathologic findings on biopsy show a pattern of infiltration of abnormal, homogenous, medium-sized lymphocytes of the hepatic sinusoids and splenic red pulp. HSTCL usually arises from a $CD4^-/CD8^-$ T-cell, and in ~15% of cases $CD4^-/CD8^+$ T-cell[15]. It is uncommon to diagnose HSTCL on bone marrow biopsy alone due to the often subtle involvement. Bone marrow involvement can range from subtle infiltrates only detected by immunostains to 70% marrow involvement. The initial marrow biopsy specimens are commonly hypercellular with trilineage hyperplasia that may be confused with a myelodysplastic or myeloproliferative syndrome[14]. Marrow involvement may increase with disease progression. Marrow infiltration may be slight, and difficult to recognize in routinely fixed specimens, making immunohistochemical staining necessary to demonstrate involvement. Flow cytometry analysis can also demonstrate an aberrant T-cell subpopulation, as in this case.

Hepatosplenic T-cell lymphoma was originally proposed as a distinct clinical entity based on the aforementioned clinical presentation and histologic involvement, but also due to the expression of γδ T-cell receptor by tumor cells[1]. Human γδ T-lymphocytes represent a normal subset of postthymic T-cells with cytotoxic function and preferential homing in some epithelial-rich tissues and within the sinusoidal area of the splenic red pulp. These γδ T-cells are not MHC restricted in their function and represent a first line defense against bacterial peptides at epidermal and epithelial surface and represent 10-12% of lymphocytes in the spleen[16]. Recently there have been several cases of HSTCL with αβ T-cell receptor phenotype as opposed to γδ receptor[11,12]. These cases of HSαβTCL have a propensity to occur in women over men, whereas HSγδTCL has a male:female ratio of ~5:1. There is also a greater age distribution in HSαβTCL. The difference in T-cell receptor however does not change the clinical presentation or course, and the World Health Organization now considers HSαβTCL an immunophenotypic variant of the same disease entity[15]. Our case likely represented HSγδTCL, given the male sex and the young age, however, further characterization was not possible due to the small biopsy specimen.

This is an aggressive lymphoma with a poor outcome. Treatment options have included anthracycline based CHOP-like regimens, alkylating agents, corticosteroids, purine analogues, and autologous and allogeneic stem cell transplant[8]. In those few patients with clinical response, there is typically early relapse. There may be an increase in median survival of up to 6 months for those patients who undergo splenectomy (either diagnostic or therapeutic) but ultimately all reported cases have died within 1-2 years despite varied therapeutic options[5]. This case report of hepatosplenic T-cell lymphoma described the characteristics of a young man presenting with massive splenomegaly and hepatomegaly without lymphadenopathy. This case's elusive findings make diagnosis challenging, and should be included in the differential diagnosis of hepatosplenomegaly.

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